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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	

ART UNIT	PAPER NUMBER
1652	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,135	PTITSYN ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-6 is/are pending in the application.

4a) Of the above claim(s) 4-6 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 22 June 2001 is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4,9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-6 are pending.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-3, drawn to a mutant N-acetylglutamate synthase, classified in class 435, subclass 193.

II. Claims 4-6, drawn to a DNA, an *E. coli* cell transformed with the same, a method of use of said cell for producing L-arginine, classified in class 435, subclass 114.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are patentably distinct because a polypeptide (enzyme) and a DNA are different compounds each with its own chemical structure and function, and they have different utilities. A DNA molecule of invention II is not limited in use to the production of a polypeptide of invention I and can be used as a hybridization probe, and a polypeptide of invention I can be obtained by a materially different method such as by the chemical synthesis.

During a telephone conversation with Dr. Daniel Pereira on June 23, 2003 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-3. Affirmation of this election must be made by applicant in replying to this Office action. Claims 4-6 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(l).

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The use of a trademark has been noted in this application (for example, "Pyrobest™" on page 14, line 8). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 3 is drawn to "The mutant N-acetylglutamate synthase according to claim 1, which includes deletion, substitution, insertion, or addition of one or several amino acids at one or plurality of positions ...". The independent claim 1 is drawn to "a mutant N-acetylglutamate synthase wherein the amino acid sequence corresponding to positions from 15 to 19 in a wild type N-acetylglutamate synthase is replaced". Claim 1 does not encompass additional modifications, i.e. deletions, substitutions, insertions, or additions of one or several amino acids, of the wild type amino acid sequence recited in claim 3.

Claim 2 is objected to because of the following informalities: as a dependent claim, claim 2 should recite "the wild type" not "a wild type". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, with dependent claim 3, is directed to a mutant N-acetylglutamate synthase wherein the amino acid sequence corresponding to positions from 15 to 19 in a wild type N-acetylglutamate synthase (NAGS) is replaced with any one of SEQ ID NOs: 1-4, and feedback inhibition by L-arginine is desensitized.

Therefore, these claims recite a genus of wild type N-acetylglutamate synthases from any source, including but not limited to bacteria, yeast and mammals. Furthermore, claim 3 recites a genus of N-acetylglutamate synthase mutants having amino acid sequences which include deletion, substitution, insertion, or addition of one or several amino acids at one or plurality of positions other than positions 15 to 19 of a specific wild type NAGS. Since the number of allowed mutations is not limited in terms of the mutant's sequence homology to the wild type amino acid sequence, this amounts to any structure and negates the relation to the specific wild type. Claim 2 is limiting the

wild type NAGS to that of *E. coli*. In its turn, *E. coli* comprises various species (strains) having different sequences (e.g., Hayashi et al. DNA Research, 8, 11-22, February 28, 2001).

The specification does not contain any disclosure of the structures of all mutant N-acetylglutamate synthases containing any one of SEQ ID NOs: 1-4 that are desensitized to feedback inhibition by arginine. The genus of claimed mutants comprises mutants derived from NAGS of different structures obtained from different sources. In addition, claim 3 encompasses mutants derived from the same wild type NAGS by an unlimited number of additional mutations, *supra*. The genus of mutants that comprise these molecules is a large variable genus comprising many structurally diverse proteins. The specification teaches only a single representative species of such wild type N-acetylglutamate synthases, an N-acetylglutamate synthase from *E. coli* from which four disclosed mutants are obtained. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of being a mutant N-acetylglutamate synthase desensitized to feedback inhibition by arginine and fails to provide any structure: function correlation present in all members of the claimed genus. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Thus, one skilled in the art cannot reasonably conclude that

the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for four specific mutants disclosed in the specification, does not reasonably provide enablement for a mutant NAGS that is desensitized to feedback inhibition by arginine, said mutant NAGS obtained by replacing a 15-19 fragment in a different wild type structure or said mutant NAGS having additional modifications in the wild type structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutants broadly encompassed by the claims, *supra*.

The specification teaches four mutants with the requisite properties obtained from a single wild type *E. coli* sequence. The specification does not teach any NAGS mutants that comprise in addition to the requisite mutations additional mutations and exhibit the requisite property. Further, it fails to provide information regarding other combinations of substitute amino acids that would result in a mutant with the requisite characteristics. While there is a great number of possible mutants, it is *a priori* unpredictable as to which mutant will exhibit the claimed property. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The amino acid sequence of a protein determines its structural and functional properties, and predictability of what changes in the amino acid sequence can be tolerated and result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of peptide mutants where

the expectation of obtaining similar activity is unpredictable based on the instant disclosure. Therefore, one of ordinary skill would require a further guidance in order to make a mutant NAGS with the requisite property other than four disclosed NAGS mutants in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has not provided the amino acid sequence of the wild type NAGS from *E. coli.* Said sequence is necessary for one to determine the recited positions 15 and 19 and therefore, to define the metes and bounds of the claims. The mere reference to this essential material by reference to a publication as made in the specification (page 6, lines 14-16) is improper.

Conclusion

The art made of record and not relied upon is considered pertinent to applicant's disclosure. EP 1170 361 A2 is an European counterpart of the instant application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

June 26, 2003